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Nitrous Oxide

Class: General Anesthetic

Risk Factor: C

FETAL RISK SUMMARY

RECOMMENDATION: Human and Animal Data Suggest Risk

Nitrous oxide (N_2O; Laughing Gas) is a nonflammable, nonexplosive gas that is widely used as an analgesic and general anesthetic. It is always administered with at least 20% oxygen

to prevent hypoxia. The blood-gas coefficient is relatively low (0.47) as is tissue solubility (brain-gas coefficient 0.50) (1).

Animal Studies

In a 1967 study, pregnant rats were exposed to 45%–50% nitrous oxide for 2, 4, or 6 days starting on gestational day 8 (2). Compared to nonexposed controls, there was a dose-related increase in embryonic death and resorptions, growth retardation, and skeletal malformations (vertebrae and ribs), and the male–female sex ratio of surviving fetuses was lower (2). Resorptions and fetal deaths were significantly increased in rats exposed to nitrous oxide (0.1% or 1.5%) mixed with oxygen for 8 or 24 hours per day for several days during midgestation (3). A lower concentration (0.01%) had no effect on the incidence of resorptions but did increase the number of fetal deaths.

A 1978 study did not observe teratogenic effects, changes in surviving fetal sex ratio, or increased fetal loss in pregnant rats exposed 8 hours per day throughout gestation to nitrous oxide (1%, 10%, or 50%) or nitrous oxide (10%) plus halothane (0.16%) (4). However, fetal growth retardation was observed in all four groups exposed to nitrous oxide. Exposure of pregnant rats to 50% nitrous oxide for 25 minutes per day for 3 consecutive days in mid-gestation resulted in an increase in fetal death rate, but no effects on fetal growth were observed (5). In another study, pregnant rats were exposed to nitrous oxide either alone (0.005% or 0.05%) or a mixture of nitrous oxide (0.05%) and halothane (0.001%) for 7 hours per day during the first 15 days of gestation (6,7). No adverse embryo or fetal effects were observed.

Continuous exposure of gravid rats to nitrous oxide (0.5%) from gestational day 1 to day 19 resulted in a significant increase in the incidence of resorptions, growth retardation, and skeletal anomalies, and a lower male-female sex ratio of surviving fetuses (8). In a follow-up to this study, the threshold dose required to produce some of these effects was determined using exposures of 0.0, 0.1%, 0.05%, and 0.025% (9). Only the group exposed to 0.1% had an increased incidence of resorptions and growth retardation. The same group of investigators reported a third study in which gravid rats were intermittently exposed (6 hours per day, 5 days per week) to nitrous oxide 0.0, 0.025%, 0.05%, 0.1%, and 0.5% throughout gestation (10). A significant reduction in litter size was noted only in the highest exposure group, but no signs of fetal resorption or skeletal malformations were found in any group.

Pregnant hamsters were exposed to nitrous oxide (70%–95%) mixed with oxygen for 24 hours during

organogenesis (11). An increased incidence of fetal death was only observed at concentrations of 90%–95%, but hypoxia-induced mortality could not be excluded. A small but significant number of fetuses had malformations (cleft palate, limb defects, gut herniation, and fetal edema), but a dose-effect relationship was not observed (11). The effects on pregnant hamsters from exposure to a combination of nitrous oxide (60%) and halothane (0.6%) for 3 hours per day on gestational days 9, 10, or 11 was reported in 1974 (12). No effects were noted on the sex ratio of surviving fetuses. Compared to controls, resorptions were increased on day 11, and decreased fetal weight was noted in the groups exposed on days 10 and 11 (12).

In a 1980 study, pregnant rats were exposed to nitrous oxide (70%–75%) or xenon (70%–75%) for 24 hours on gestational day 9 (13). Compared to controls and the xenon-exposed group, the nitrous oxide group had a significant increase in the incidence of resorptions and congenital malformations (delayed maturation of the skeletal system, fused ribs, encephalocele, hydrocephalus, anophthalmia, microphthalmia, gastroschisis, and gonadal agenesis) (13). The above experiment was repeated by another group with four different

concentrations of nitrous oxide: 0.75%, 7.5%, 25%, and 75% (14). The threshold for toxicity was determined to be greater than 25% because only those animals exposed to the 75% concentration had increased incidences of resorptions and both major and minor congenital malformations. However, all exposures caused a significant increase in minor variants involving the ribs and sternum (14).

In another study by the above investigators, the effect of nitrous oxide in pregnant rats was compared to three other general anesthetic agents (see also Enflurane, Halothane, and Isoflurane) (15). The nitrous oxide dose was 75% (0.55 MAC). (*Note: the minimum alveolar anesthetic concentration [MAC] is the concentration that causes immobility in 50% of patients exposed to a noxious stimulus such as a surgical incision; it represents the* ED_{50} *[16].*) Each agent was administered for 6 hours on each of three consecutive days in one of three periods: gestational days 8–10, 11–13, or 14–16. Compared with controls, significantly decreased maternal weight gain was observed in three of the groups (nitrous oxide, isoflurane, and enflurane) after exposure on days 14–16. Exposure on those days resulted in significantly decreased fetal weight in all four groups, and when exposure occurred on days 8–10, in three groups (all except nitrous oxide). Nitrous oxide exposure during days 14–16 resulted in significant increases in total fetal wastage and resorptions (3-fold increases). However, no major or minor congenital defects were observed in any of the groups (15).

No evidence of reproductive toxicity was observed in mice exposed to nitrous oxide (0.5%, 5%, or 50%) for 4 hours per day on days 6–15 of gestation (17). In the same experiment, the fertility of male mice exposed in the same way for 9 weeks was not affected. Based on their previous work, they concluded that the order of reproductive toxicity was halothane > enflurane > methoxyflurane > nitrous oxide (17). Of interest, a 1990 study found that brief exposure of 2-cell mouse preimplantation embryos to nitrous oxide/oxygen (60%/40%) caused disruption to subsequent embryo cleavage and blastocyst development (18).

A 1989 study determined the susceptible period for nitrous oxide teratogenicity in rats (19). Pregnant rats were exposed to 60% nitrous oxide for 24 hours on each of gestational days 6–12. There were no differences among the seven groups in the number of live fetuses, fetal weight, and sex ratio. However, compared to controls, there was a significant increase in the mean percentage of resorptions/litter and number of litters with resorptions on days 8 and 11. Major skeletal anomalies (ribs and vertebrae) were increased only on day 9, but minor skeletal defects were increased on days 8 and 9. Right sided aortic arch and left sided umbilical artery, defects indicative of altered laterality, were increased on day 8 and hydrocephalus was increased on gestational day 9 (19).

A 1986 mouse study tested the hypothesis that prenatal nitrous oxide exposure (75% with 25% oxygen for 6 hours on gestational day 14) or postnatal exposure (same mixture for 4 hours on postnatal day 2) would cause permanent damage to the developing brain and behavioral effects (20). Compared to

controls, offspring (postnatal day 6 to 6 months of age) exposed prenatally or postnatally were noted to have several abnormal behavioral effects that included preweaning motor development and general activity. When they reached adulthood, their brains were also noted to have significant morphologic changes (20). A 1986 rat study also found that *in utero* exposure caused permanent alterations in the spontaneous motor output of the brain that affected females more than males (21). By using a slightly different exposure protocol during rat pregnancy, these same investigators did observe subtle differences from controls in growth rates at 14 and 21 days and reduced reflex suspension, indicating that normal development had been interrupted (22). In a

fourth study, mouse offspring exposed *in utero* to nitrous oxide during organogenesis had hyporeactivity of the startle reflex at 60 and 95 days of age (23).

The effects of nitrous oxide on growing neural tips (growth cones) in the forebrains of neonatal rat pups were described in a 1993 report (24). The pups were exposed to three concentrations of nitrous oxide (25%, 50%, and 75%) over a 6-hour period on postnatal day 1. A dose-response on the activity of a growth cone enzyme (protein kinase C, PKC) was found, with the lowest concentration having no effect on the enzyme. The 75% concentration, however, reduced the activity to about 63%. The 50% dose also reduced the PKC activity but to a lesser degree. The authors thought that the reduced enzyme activity could be related to long-term morphologic or behavioral neuroabnormalities in the pups (24).

The effect of nitrous oxide on rat fertility was described in a 1990 study (25). Adult virgin female rats were exposed to the gas during their 4-day ovulatory cycles. Nitrous oxide disrupted luteinizing hormone releasing hormone (LHRH) (now known as *gonadotropin-releasing hormone*) cells in the hypothalamus. This disruption resulted in the inhibition of LHRH release and, thus, ovulation (25).

Human

Placental Passage

Nitrous oxide rapidly crosses the human placenta to the fetus, thereby obtaining amounts in the fetal circulation nearly equivalent to those in the mother (26,27,28,29,30,31). In a 1970 study, umbilical vein and artery nitrous oxide concentrations ranged up to 91% of maternal levels and increased progressively with increasing duration of anesthesia (27).

Spontaneous Abortion

A number of reports have described the association between spontaneous abortions (SABs) and exposure to anesthetic gasses in the operating room, dental office, or during surgery (32,33,34,35,36,37,38,39,40,41,42,43,44,45,46). In addition, several reviews have examined this topic (47,48,49,50,51,52,53,54,55).

The principal concern for chronic exposure to anesthetic gasses relates to unscavenged environments in which high concentrations of gases, such as nitrous oxide, have been measured. A 1972 reference cited studies that measured levels of nitrous oxide in the operating room averaging 130 ppm (0.013%) but with peak concentrations as high as 428 ppm (0.048%) (32). Even higher levels (e.g., 9700 ppm or 0.97%) were measured in the anesthesiologist's inhalational zone. A 1970 report described the results of a survey from a group of nurses (67 operating room/92 general duty) and physicians (50 anesthetists/81 specialists other than anesthesia) that were routinely exposed to anesthetics in the operating room (33). In the first group, 29.7% of the pregnancies of operating room nurses ended in SAB, compared to 8.8% in the controls. In the second group, the SAB incidence was 37.8% and 10.3%, respectively. In both exposed groups, the SAB occurred earlier than the controls (8th vs. 10th week). However, the study could not identify a specific anesthetic agent, nor could it establish a cause-effect relationship (33).

The results of a national survey of operating room personnel was reported in 1974 (34). The survey

included the memberships of four organizations, essentially covering all personnel in the United States who were continuously exposed to low levels of anesthetic gasses: American Society of Anesthesiologists (ASA), American Association of Nurse Anesthetists (AANA), Association of Operating Room Nurses (AORN), and Association of Operating Room Technicians (AORT). Two control groups were surveyed: American Academy of Pediatrics (AAP) and American Nurses Association (ANA). At the time of the survey, about 21% of the operating rooms were ventilated and anesthetic-scavenged. The rates of SAB

among the respondents (organization and total number of pregnancies shown in parentheses) were 17.1% (ASA; 468), 17.0% (AANA; 1826), and 19.5% (AORN/AORT; 2781). The results were statistically significant when compared to women working outside of the operating room. However, no difference was found with the controls for the time (in gestational weeks) of the abortions or for a decrease in the sex ratio of exposed pregnancies (34).

A survey of women physicians in England and Wales to determine the outcome of pregnancies was reported in 1977 (35). The analysis involved 9044 pregnancies that were classified into three groups: working anesthetists (*N* = 670), other medical specialties (includes medical students but excludes radiologists) (*N* = 6377), and physicians not currently working (*N* = 1997). The adjusted SAB rates were 13.8%, 13.8%, and 12.0%, respectively. For stillbirths, the rates were 17.3%, 8.3%, and 10.3% (*n.s.*), respectively (35). Another survey in England of anesthetists exposed to anesthetics, male and female, appeared in 1979 (36). The SAB rates (percentage of known conceptions) for exposed fathers, mothers, both parents, and nonexposed controls were 15.7%, 34.4%*, 23.1%*, and 9.8%, respectively (*significant compared to controls).

Because dentist and their assistants may be exposed to even higher concentrations of anesthetic gases than personnel in hospital operating rooms, a survey of this population was undertaken and reported in 1980 (37). The responding sample size involved more than 22,000 dentists (98.5% male) and more than 21,000 chairside assistants (99.1% female). Only about 19% of the individuals were exposed to halogenated anesthetic gases in addition to nitrous oxide. The two groups were further classified by the amount of exposure in the year before conception (nonusers, light [1–2999 hours in past decade], and heavy [more than 3,000 hours in past decade]). After adjustment for smoking, age, and pregnancy history, a significant association was found between use of anesthetics and the rate of SAB in chairside assistants (8.1% nonusers, 14.2% light, and 19.1% heavy). The association also was significant for wives of dentists but the rates of SAB were about half of those for the assistants (37). In a brief 1986 report, six SABs were observed in four female personnel over a 17-month interval (38). These persons worked in an oral surgery department that used 35% nitrous oxide in oxygen as a sedative during procedures. In the operating rooms, the range of nitrous oxide concentrations were 0.01–0.04% but were as high as 0.07% when the patient talked (38). A 1995 study found a significant increase in SAB among female dental assistants who worked for 3 or more hours per week in offices not using scavenging equipment (39). After adjustment for age, smoking, and number of amalgams prepared, the relative risk (RR) was 2.6 (95% confidence interval [CI] 1.3–5.0).

In contrast to the above reports, two studies found no association between chronic exposure to nitrous oxide and SAB, and a third found only a partial association (40,41,42). In comparison to unexposed controls, the adjusted odds ratios (ORs) for SAB in dental assistants working in unscavenged clinics or dental school services in Denmark were 0.9 (95% CI 0.4–2.1) and 0.3 (0.0–1.8), respectively (40). In a Swedish study of 1711 midwives, the use of nitrous oxide (>50% of deliveries) was not associated with an increased risk of SAB (OR 0.95, 95% CI 0.62–1.47) (41). The study could not determine if scavenging equipment for waste gas was used. The investigators concluded that night work and high workload increased the risk of SAB (41). In an earlier study, the rates of SAB were compared for 563 married female anesthetists, working and not working, to 828 female physician controls (42). The rates were 18.3%, 13.7%, and 14.7%, respectively.

A 1980 report described the outcomes of 187 women who had been exposed to inhalational

anesthetics (mostly nitrous oxide) during work or by their husbands, and who

had surgery during pregnancy (43). The study was an extension of the study involving occupational exposure to inhalational anesthetics and SAB in wives of dentists and dental assistants (*N* = 12,929) (see reference #37). The rates of 1st trimester SAB in four groups classified as controls (*N* = 8654; no exposure or surgery), exposure/no surgery (*N* = 4088), no exposure/surgery (*N* = 122), and exposure/surgery (*N* = 65) were 5.1%, 8.6%, 8.0%, and 14.8%, respectively. The rates for 2nd trimester SAB were 1.4%, 2.6%, 6.9%, and 0, respectively (43). A Canadian study compared pregnant women who where undergoing incidental surgery with pregnant women not undergoing surgery (44). Surgery (usually gynecologic) under general anesthesia in the 1st or 2nd trimesters was associated with an increased risk of SAB (estimated risk ratio [ERR] 2.0, 95% CI 1.10–3.64). The risk was also increased following procedures under general anesthesia that were remote from the conceptus (ERR 1.54, 95% CI 1.03–2.30) (44). A 1986 study in 433 women (9 sets of twins) of general anesthesia with nitrous oxide given in the 1st and 2nd trimesters was unable to find an association between the anesthetic and SAB (45).

Finally, a 1985 study combined the data from six studies to determine the risk of SAB in operating room personnel (46). The low RR was 1.3 (95% CI 1.2–1.4) for pregnant physicians and nurses.

Infertility – Female

An increased rate of infertility in anesthetists was noted in a 1972 study (42). In this survey of women anesthetists in the United Kingdom, 65 (12%) of the 563 married anesthetists reported infertility of unknown cause compared to 6% of controls. However, 36 (44%) eventually conceived, even though 92% of them continued to work (42). A 1979 survey reported that 30% of anesthetists (includes both sexes) had difficulty in conceiving, but unexpected infertility occurred in only 3% (37).

A 1992 study examined the effect of environmental nitrous oxide on the fertility of dental assistants (56). A group of 7000 female dental assistants was surveyed, and 459 were determined to be eligible for the study because they had met all inclusion criteria, including conception, within the previous 4 years. Of those eligible, 418 (91%) completed the telephone interview. Data were collected over 13 menstrual cycles (about 1 year). The primary statistical analysis involved a comparison of the adjusted fecundability ratio (an estimate of the conception rate for exposed women relative to that for unexposed women in each menstrual cycle of unprotected intercourse) (56). No difference in the ratio was observed in the 121 assistants who worked <5 hours/week (*N* = 85; ratio 1.05) or ≥5 hours/week (*N* = 36; ratio 1.15) in scavenged offices. In contrast, among the 60 assistants who worked in unscavenged offices, the 41 working <5 hours/week had a significantly higher adjusted ratio (1.01) than the 19 working ≥5 hours/week (0.41). Thus, the latter group was only 41% as likely as unexposed women to conceive during each menstrual cycle. In addition, the study examined the occurrence of SAB. Among the 325 pregnancies (93 excluded because they were pregnant at the time of data collection), 10 were in the “high exposure” unscavenged group. Their SAB rate was 50% (5/10), whereas 25 (8%) of the remaining 315 pregnancies aborted (56). An accompanying editorial and later correspondence discussed the implications of the study (57,58,59,60,61).

A 1996 study involving Swedish midwives obtained results similar to those above (62). As in the above study, data were collected over 13 menstrual cycles. In 84% of the responders (*N* = 3985) to a mailed questionnaire, the adjusted fecundability ratios of three groups, compared to those working in the day time, were two-shift rotations 0.78, three-shift rotations 0.77, night-shift only 0.82, respectively. The effect of nitrous oxide was noted only for midwives exposed to more than 30 deliveries/month where the gas was used (ratio 0.64) (62).

The effects of general anesthesia on pregnancy rates in patients who were undergoing embryo transfer after *in vitro* fertilization were described in a 1995 study (63). Analgesia for ovum retrieval and embryo transfer was sedation (opiates, diazepam, promethazine)/local anesthesia (120 cycles; 88

patients), epidural block (139 cycles; 111 patients), and general anesthesia (nitrous oxide, halothane, opiates, and barbiturates) (173 cycles; 112 patients). The groups did not differ in embryo yield or number or quality of embryos transferred. However, the clinical pregnancy rates for the general anesthesia group were significantly lower than that for the other two groups: 25.8%, 23.7%, and 14.5%, respectively. The delivery rate also was significantly lower for the general anesthesia group: 19.2%, 20.1%, and 8.7%, respectively. The authors concluded that the adverse effect of general anesthesia occurred after embryo transfer and was probably related to nitrous oxide exposure (63). However, a 1999 study with data from seven fertility programs involving gamete intrafallopian transfer found no significant difference in the clinical pregnancy or delivery rates between women who had received nitrous oxide (or other anesthetic agents) and those who did not (64).

Infertility – Male

A survey of 5507 male anesthetists in the United Kingdom found no association between paternal work in operating rooms and SAB, infertility, or the frequency of congenital anomalies (65). However, if the mother was also exposed, the risk of SAB may be increased by 158% to 271%. A 1987 review suggested that male fertility could be affected by direct nitrous oxide inactivation of vitamin B_{12} (cyanocobalamin) (66). The inactivation of this vitamin could result in a reduction of methionine synthetase that is essential for normal cell division (66). A later review discussed the effect of nitrous oxide on cyanocobalamin-dependent methionine synthetase and other factors that eventually impair DNA synthesis and could cause infertility (67).

Congenital Malformations

Several studies have examined the relationship between 1st trimester exposure to nitrous oxide and congenital malformations (34,35,36,42,43,44,45,46,68,69,70,71,72,73,74). Two early studies did not find such a relationship, but the number of exposed cases was small (68,69). A larger study also found no relationship between surgical anesthesia and congenital malformations (44). In another previously cited study, the overall rate of birth defects in live-births was no different in 583 anesthetists (5.2%) and 828 controls (4.9%) (42). However, when analyzed separately, working anesthetists had a significantly higher rate of offspring with defects (6.5%) than those who were not working (2.5%), but not significantly higher than controls.

A 1974 survey of 621 female nurse-anesthetists, with a response rate of 84.5%, found an incidence of birth defects (major and minor) in offspring of working mothers of 16.4%, compared to 5.7% when the mother was not working (70). Nearly one half of the defects in the exposed group were cutaneous anomalies. In the 1974 national survey cited above, the congenital abnormality rates (all skin anomalies were excluded) in the groups (unexposed vs. exposed) were ASA (3.4% vs. 5.9%), AANA (5.9% vs. 9.6%), and AORN/AORT (7.0% vs 7.7%) (34). The first two comparisons were statistically significant. The survey also provided the congenital malformation rates (excluding skin anomalies) for wives of the male survey respondents in the three groups: 5.4%, 8.2%, and 6.4%, respectively (34). A 1977 survey found a significant rate of heart/great vessel defects in working anesthetists (13.8%), in comparison to a combined group of other physicians (3.6%), or an earlier population-based study (6.6%) (35). However, no differences were found for other congenital anomalies (neural tube defects [NTD], oral clefts, talipes, congenital hip dislocation, hydrocele, hypospadias, and epispadias, and genitourinary). The rates of development or

congenital abnormalities (percentage of live births) in a 1979 survey of anesthetists exposed to anesthetics were 9.3% (*N* = 22) for exposed fathers, 4.8% (*N* = 1) for exposed mothers, and 15.0% (N = 3) when both parents were exposed (36). These rates did not differ significantly from nonexposed controls.

No significant increase in the incidence of birth defects was found in a 1980 study of surgery during early pregnancy (43). Anesthetics for surgery were used in 187 women during the 1st trimester and in 100 women during the 2nd trimester. The rates of defects in the offspring of mothers who had surgery

in the 1st and 2nd trimesters, but no occupational exposure to inhalational anesthetics, were 3.1% and 5.8%, respectively. For surgery plus occupational exposure, the rates were 7.2% and 2.3%, respectively. The differences were not significant (43). A 1986 study analyzed the outcomes of 375 cases (8 sets of twins) of cervical cerclage and 58 other surgeries (1 set of twins) conducted under general anesthesia with nitrous oxide (45). Cases were further stratified by the gestational week when surgery was conducted (>16 weeks or ≤16 weeks). None of the observed birth defects could be attributed to anesthetic exposure (45). A 1985 study combined the results from six studies to derive an RR for congenital abnormalities of 1.2 (95% CI 1.0–1.4) for pregnant physicians and nurses working in operating rooms (46).

Using data from three Swedish health care registries for the years 1973 to 1981, a 1989 study analyzed 5405 cases of nonobstetric surgical operations that occurred during pregnancy (71). The types of anesthesia were general (about 54%; 99% using combinations with nitrous oxide), regional (about 14%), and unknown (32%). The rates of congenital malformations, stillbirths, infant death within 7 days of birth, and decreased birth weights were determined by the trimester in which the operation was performed. For congenital malformations, the RR and 95% CI for the 1st, 2nd, and 3rd trimesters and the total group were 1.0 (0.8–1.4), 0.9 (0.6–1.2), 1.5 (1.1–2.2) and 1.1 (0.9–1.3), respectively. The rate for all defects was about 5%; about 1.9% for major anomalies. Both rates were similar to those in the total Swedish population. The risk for stillbirths also was not significantly different from the general population (RR 1.4, 95% CI 1.0–1.8), but the risk of infant death within 7 days of birth was increased (RR 2.1, 95% CI 1.6–2.7). Most of the infant deaths (70%) occurred in infants of very-low-birth-weight. The rates of low-birth-weight (<2500 g) and very-low-birth-weight (<1500 g) infants were increased in all trimesters and for the total the RR (95% CI) were 2.0 (1.8–2.2) and 2.2 (1.8–2.8). The reduced weights were due to prematurity and intrauterine growth retardation. For all mothers who were operated on, the prematurity rate was 7.47% vs. 5.13% in controls (p < 0.001) (71).

Using the same data as in the above study, study investigators found a possible association between surgery in the 1st trimester and NTD, and these findings were published in 1990 (72). The investigators studied 2252 infants whose mothers had surgery during the 1st trimester. Six of the infants had NTD (expected 2.5), one of whom was thought to have Meckel's syndrome. An additional infant had a diagnosis of hydranencephaly, but the autopsy report indicated the diagnosis was uncertain and it may have been a very large encephalocele. In the total group, 572 had operations during the period of neural tube closure (gestational weeks 4 and 5). Mothers of five of the six infants with NTD (expected 0.6) had surgery during this period, but only three had been exposed to nitrous oxide. The mother of the hydranencephaly case had surgery in gestational week 8 and was not exposed to nitrous oxide. The authors could not determine whether the findings represented a causal association with surgery or just a random occurrence (72).

In a 1994 population-based, case-control study, 12 (1.7%) of 694 mothers of infants with central nervous system (CNS) defects had surgery under general anesthesia in the 1st trimester, compared to 34 (1.1%) of 2984 controls (73). Analysis of total CNS defects

and 1st trimester exposure to general anesthesia revealed the following: NTD (345 cases; 3 exposed), OR 0.7, 95% CI 0.2, 2.4; microcephaly (91 cases; 1 exposed), OR 1.7, 95% CI 0.2, 13.5; hydrocephalus (198 cases; 7 exposed), OR 3.8, 95% CI 1.6, 9.1. When isolated CNS defects were analyzed, the OR and 95% CI for the three defects were 1.1 (0.3, 4.9), 3.8 (0.4, 33.0), and 0.0 (0.00, 4.1) (all nonsignificant). However, when the analysis included multiple CNS defects, there were 70 cases (7 exposed) of hydrocephalus (OR 9.6, 95% CI 3.8, 24.6), 8 cases (3 exposed) of hydrocephalus and eye defects (OR 39.6, 95% CI 7.5, 209.2), and 2 cases (2 exposed) of hydrocephalus and cataracts (OR infinity, 95% CI 1329, infinity). Although the investigators identified several limitations of their study, including the inability to identify the specific medications used for general anesthesia, the findings do warrant additional study (73).

The Collaborative Perinatal Project monitored 50,282 mother-child pairs, 76 of whom were exposed to nitrous oxide during the 1st trimester (74). Four malformed infants were observed, a hospital standardized relative risk of 0.75. There was no evidence of an association between the gas and the defects (74).

Neurotoxicity

The mechanism of action of nitrous oxide, at anesthetic concentrations, is thought to involve blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors (75,76,77,78,79). This action also produces neurotoxic effects, which can be prevented by drugs (e.g., benzodiazepines, barbiturates, halothane, isoflurane, propofol, scopolamine, and atropine) that enhance GABAergic (γ-amino-n-butyric acid) inhibition (75,77). However, the addition of ketamine, another NMDA antagonist, to nitrous oxide without concomitant use of a GABA agonist has been shown in animals to potentiate the neurotoxicity of nitrous oxide (80). Recent evidence has shown that the neurotoxicity of ethanol, a NMDA antagonist and a potentiator of GABA transmission, is different in immature brains than in adult brains (81). Therefore, the potential exists that the common use of nitrous oxide and GABAergic agents together during general anesthesia in obstetrics and pediatrics could cause neuroteratogenicity during human brain growth spurts (synaptogenesis; 3rd trimester to several years after birth) (81,82,83). Animal studies in 7-day-old rats have demonstrated this teratogenicity, as evidenced by widespread apoptotic neurodegeneration, deficits in hippocampal synaptic function, and persistent impairment of memory and learning (84).

A 2004 study examined the association between exposure of mothers to waste anesthetic gases during pregnancy and development of their offspring (85). Although the specific gases were not identified, the timing of the exposures (1983–1996) and practice patterns suggested that nitrous oxide, halothane, and isoflurane were the most likely agents. Forty children (age 5–13 years) born to female anesthesiologists and operating room nurses who were exposed to waste anesthetic gases were compared to 40 female physicians and nurses (matched for children's age, gender, and maternal occupation) who worked in hospitals during their pregnancies but who did not work in operating rooms (unexposed controls). All children underwent standardized developmental tests to evaluate their medical and neurodevelopmental state and the mothers were interviewed. The developmental milestones in the two groups were similar, but the exposed children had a significantly lower gross motor ability and more evidence of inattention/hyperactivity. Moreover, the level of exposure was significantly and negatively correlated with fine motor ability and IQ performance. The investigators concluded that the results supported the hypothesis that occupational exposure to waste anesthetic gases during pregnancy might be a risk factor for minor neurological deficits in the offspring (85).

Miscellaneous Effects

Subanesthetic doses of nitrous oxide have been used for analgesia in laboring patients (86,87,88,89,90,91,92,93). The effects on the fetus do not appear to be any different from those of other general anesthetics (92). When used as an analgesic, nitrous oxide has no direct effect on uterine activity (87,94). In contrast, prolonged general anesthesia with nitrous oxide may cause neonatal acidosis and an increased incidence of low Apgar scores (95). A 1988 study concluded that the use of high intermittent doses of nitrous oxide used for obstetric analgesia was associated with a risk of developing amphetamine addiction in later life (96). The mechanism was thought to be an effect of imprinting. However, this study has been criticized for several design flaws and conclusions (88).

A 2-minute inhalation dose of 30% nitrous oxide with oxygen for analgesia at term resulted in a decrease in both maternal and fetal central vascular resistance (97). Although this dose is usually safe for the mother or fetus, the cerebral hyperemia induced by nitrous oxide might increase the risk of intracranial hemorrhage in preterm infants (97).

Decreased birth weight, but not preterm birth, was associated with occupational exposure to nitrous oxide in a 1999 study based on a survey of the Swedish Midwifes Association (98). Chronic nitrous oxide exposure during the 2nd trimester was associated with 77 g decrease in birth weight (95% CI 129, 24) and an increase in the odds of infants being small-for-gestational-age (OR 1,8, 95% CI 1.1, 2.8) (99). In a 1977 survey, the offspring of working anesthetists had significantly lower birth weights and a higher proportion of infants weighing 2500 g or less than did two other physician groups (35). Lower birth weights also were observed in offspring of female anesthetists in a 1979 survey (36). Female infants were particularly under weight. Moreover, there was a lower male:female sex ratio in the offspring of female anesthetists (36). The author, however, has had to defend his research (99).

A 1991 population-based case-control study conducted in Sweden found an association between childhood leukemia and nitrous oxide anesthesia during delivery (100). Mothers of the 411 cases were more likely than controls to have received the anesthetic (OR 1.3, 95% CI 1.0, 1.6).

Summary

A large amount of data has been published concerning the reproductive toxicity of nitrous oxide. Abortions and growth retardation have been consistently observed in animal studies, but the exposures to the gas were usually much higher and of greater duration than the exposures that occur in humans. Structural anomalies, usually involving the skeleton, were inconsistently found. Neuroteratogenicity also has been noted in animal studies and, in some cases, permanent changes in the brains of animals exposed *in utero* have been found. Thus, in animals, nitrous oxide is an embryo and fetal toxin that may have long-lasting consequences.

The evidence for human reproductive toxicity is not as clear. Much of the data relating to SAB, infertility, and decreased birth weight is based on voluntary responses to surveys that involved self-reported outcomes. These retrospective reports are subject to self-selection and/or recall bias. Moreover, many studies have evaluated exposure to nitrous oxide in operating rooms or dental offices, rather than to individuals, and have not quantified the amount and type of anesthetic gas exposure (46,101). In addition, the studies have not always accounted for confounding variables, such as the introduction of scavenging equipment and ventilation, maternal age, smoking, and other drug exposures, and have characterized nitrous oxide exposure based only on job title (102). Nevertheless, there does appear to be an increase in the incidence of SAB and infertility related to chronic exposure

to nitrous oxide, but the dose and magnitude of these effects need further study. Moreover, general anesthesia in the 1st and 2nd trimesters has been associated with reduced birth weight, but the causative agents have not been identified.

The information for nitrous oxide and congenital malformations is less confusing, but many of the limitations identified above also apply to this patient population. However, the available data do not appear to suggest that acute or chronic exposure to nitrous oxide at any time in pregnancy represents a major risk for congenital anomalies. Although nitrous oxide is the most commonly used general anesthetic agent, it is never administered alone, being combined with a number of other agents. Therefore, the safest course is to postpone elective surgical procedures until after pregnancy or, at the minimum, until after the period of organogenesis. Moreover, because even operating rooms that are scavenged and ventilated are not entirely free of waste anesthetic gases, women who might become pregnant and are working in these areas should be counseled as to the potential risks and offered positions in areas free of nitrous oxide contamination. Recent data have shown that offspring of mothers with occupational exposure could have long-term neurodevelopmental deficits. Finally, long-term neurotoxicity studies of infants exposed *in utero* to nitrous oxide during the 3rd trimester or during the first few years after birth are warranted.

BREAST FEEDING SUMMARY

RECOMMENDATION: Compatible

No reports describing the use of nitrous oxide during lactation have been located. The solubility in blood and tissue is low. Moreover, the plasma half-life is very short (<3 minutes) and, thus, it is unlikely that a nursing infant would be exposed to the agent in milk or that it would be orally bioavailable to the infant (103).

References

1. Steward A, Allott PR, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesth 1973;45:282–93.

2. Fink BR, Shepard TH, Blandau RJ. Teratogenic activity of nitrous oxide. Nature 1967;214:146–8.

3. Corbett TH, Cornell RG, Endres JL, Millard RI. Effect of low concentrations of nitrous oxide on rat pregnancy. Anesthesiology 1973;39:299–301.

4. Pope WDB, Halsey MJ, Phil D, Lansdown ABG, Simmonds A, Bateman PE. Fetotoxicity in rats following chronic exposure to halothane, nitrous oxide, or methoxyflurane. Anesthesiology 1978;48:11–6.

5. Ramazzotto LJ, Carlin RD, Warchalowski GA. Effects of nitrous oxide during organogenesis in the rat. J Dent Res 1979;58:1940–3.

6. Coate WB, Kapp RW Jr, Lewis TR. Chronic exposure to low concentrations of halothane-nitrous oxide. Anesthesiology 1979;50:310–8.

7. Coate WB, Kapp RW Jr, Ulland BM, Lewis TR. Toxicity of low concentration long-term exposure to an airborne mixture of nitrous oxide and halothane. J Environ Pathol Toxicol 1979;2:209–31.

8. Vieira E. Effect of the chronic administration of nitrous oxide 0.5% to gravid rats. Br J Anaesth 1979;51:283–7.

9. Vieira E, Cleaton-Jones P, Austin JC, Moyes DG, Shaw R. Effects of low concentrations of nitrous oxide on rat fetuses. Anesth Analg 1980;59:175–7.

10. Vieira E, Cleaton-Jones P, Moyes D. Effects of low intermittent concentrations of nitrous oxide on the developing rat fetus. Br J Anaesth 1983;55:67–9.

11. Shah RM, Burdett DN, Donaldson D. The effects of nitrous oxide on the developing hamster embryos. Can J Physiol Pharmacol 1979;57:1229–32.

12. Bussard DA, Stoelting RK, Peterson C, Ishaq M. Fetal changes in hamsters anesthetized with nitrous oxide and halothane. Anesthesiology 1974;41:275–8.

13. Lane GA, Nahrwold ML, Tait AR, Taylor-Busch M, Cohen PJ, Beaudoin AR. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. Science 1980;210:899–901.

14. Mazze RI, Wilson AI, Rice SA, Baden JM. Reproduction and fetal development in rats exposed to nitrous oxide. Teratology 1984;30:259–65.

15. Mazze RI, Fujinaga M, Rice SA, Harris SB, Baden JM. Reproductive and teratogenic effects of nitrous oxide, halothane, isoflurane, and enflurane in Sprague-Dawley rats. Anesthesiology 1986;64:339–44.

16. Trevor AJ, Miller RD. General anesthetics. In Katzung BG, ed. Basic and Clinical Pharmacology. 8th ed. New York: McGraw-Hill, 2001:426.

17. Mazze RI, Wilson AI, Rice SA, Baden JM. Reproduction and fetal development in mice chronically exposed to nitrous oxide. Teratology 1982;26:11–6.

18. Warren JR, Shaw B, Steinkampf MP. Effects of nitrous oxide on preimplantation mouse embryo cleavage and development. Biol Reprod 1990;43:158–61.

19. Fujinaga M, Baden JM, Mazze RI. Susceptible period of nitrous oxide teratogenicity in Sprague-Dawley rats. Teratology 1989;40:439–44.

20. Rodier PM. Inhalant anesthetics as neuroteratogens. Ann N Y Acad Sci 1986;477:42–8.

21. Mullenix PJ, Moore PA, Tassinari MS. Behavioral toxicity of nitrous oxide in rats following prenatal exposure. Toxicol Ind Health 1986;2:273–87.

22. Tassinari MS, Mullenix PJ, Moore PA. The effects of nitrous oxide after exposure during middle and late gestation. Toxicol Ind Health 1986;2:261–71.

23. Rice SA. Effect of prenatal N_2O exposure on startle reflex reactivity. Teratology 1990;42:373–81.

24. Saito S, Fujita T, Igarashi M. Effects of inhalational anesthetics on biochemical events in growing neuronal tips. Anesthesiology 1993;79:1338–47.

25. Kugel G, Letelier C, Zive MA, King JC. Nitrous oxide and infertility. Anesth Prog 1990;37:176–

80.

26. Cohen EN, Paulson WJ, Wall J, Elert B. Thiopental, curare, and nitrous oxide anesthesia for cesarean section with studies on placental transmission. Surg Gynecol Obstet 1953;97:456–62.

27. Marx GF, Joshi CW, Orkin LR. Placental transmission of nitrous oxide. Anesthesiology 1970;32:429–32.

28. Morgan CA, Paull J. Drugs in obstetric anaesthesia. Anaesth Intens Care 1980;8:278–88.

29. Nandi PR, Morrison PF, Morgan BM. Effects of general anaesthesia on the fetus during caesarean section. Anaesth Rev 1991;8:103–22.

30. Friedman JM. Teratogen update: anesthetic agents. Teratology 1988;37:69–77.

31. Kanto J. Risk-benefit assessment of anaesthetic agents in the puerperium. Drug Saf 1991;6:285–301.

32. Corbett TH. Anesthetics as a cause of abortion. Fertil Steril 1972;23:866–9.

33. Cohen EN, Bellville JW, Brown BW Jr. Anesthesia, pregnancy, and miscarriage: a study of operating room nurses and anesthetists. Anesthesiology 1971;35:343–7.

34. Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel, American Society of Anesthesiologists. Occupational disease among operating room personnel: a national study. Anesthesiology 1974;41:321–40.

35. Pharoah POD, Alberman E, Doyle P. Outcome of pregnancy among women in anaesthetic practice. Lancet 1977;1:34–6.

36. Tomlin PJ. Health problems of anaesthetists and their families in the West Midlands. Br Med J 1979;1:779–84.

37. Cohen EN, Brown BW, Wu ML, Whitcher CE, Brodsky JB, Gift HC, Greenfield W, Jones TW, Driscoll EJ. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980;101:21–31.

38. Schuyt HC, Brakel K, Oostendorp SGLM, Schiphorst BJM. Abortion among dental personnel exposed to nitrous oxide. Anaesthesia 1986;41:82–3.

39. Rowland AS, Baird DD, Shore DL, Weinberg CR, Savitz DA, Wilcox AJ. Nitrous oxide and

spontaneous abortion in female dental assistants. Am J Epidemiol 1995;141:531–8.

40. Heidam LZ. Spontaneous abortions among dental assistants, factory workers, painters, and gardening workers: a follow up study. J Epidemiol Comm Health 1984;38:149–55.

41. Axelsson G, Ahlborg G Jr, Bodin L. Shift work, nitrous oxide exposure, and spontaneous abortion among Swedish midwives. Occup Environ Med 1996;53:374–8.

42. Knill-Jones RP, Rodrigues LV, Moir DD, Spence AA. Anaesthetic practice and pregnancy – controlled survey of women anaesthetists in the United Kingdom. Lancet 1972;1:1326–8.

43. Brodsky JB, Cohen EN, Brown BW Jr, Wu ML, Whitcher C. Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 1980;138:1165–7.

44. Duncan PG, Pope WDB, Cohen MM, Greer N. Fetal risk of anesthesia and surgery during pregnancy. Anesthesiology 1986;64:790–4.

45. Crawford JS, Lewis M. Nitrous oxide in early human pregnancy. Anaesthesia 1986;41:900–5.

46. Buring JE, Hennekens CH, Mayrent SL, Rosner B, Greenberg ER, Colton T. Health experience of operating room personnel. Anesthesiology 1985;62:325–30.

47. Spence AA, Knill-Jones RP. Is there a health hazard in anaesthetic practice? Br J Anaesth 1978;50:713–9.

48. Brodsky JB. Anesthesia and surgery during early pregnancy and fetal outcome. Clin Obstet Gynecol 1983;26:449–57.

49. Alridge LM, Tunstall ME. Nitrous oxide and the fetus. Br J Anaesth 1986;58:1348–56.

50. Eger EI II. Fetal injury and abortion associated with occupational exposure to inhaled anesthetics. AANA J 1991;59:309–12.

51. Shortridge-McCauley LA. Reproductive hazards: an overview of exposures to health care workers. AAOHN J 1995;43:614–21.

52. Donaldson D, Meechan JG. The hazards of chronic exposure to nitrous oxide: an update. Br Dent J 1995;178:95–100.

53. Sessler DI. Risks of occupational exposure to waste-anesthetic gases. Acta Anaesthesiol Scand 1997;41(Suppl 111):237–9.

54. Wasylko L, Matsui D, Dykxhoorn SM, Rieder MJ, Weinberg S. A review of common dental treatments during pregnancy: implications for patients and dental personnel. J Can Dent Assoc 1998;64:434–9.

55. Smith DA. Hazards of nitrous oxide exposure in healthcare personnel. AANA J 1998;66:390–3.

56. Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med 1992;327:993–7.

57. Baird PA. Occupational exposure to nitrous oxide—not a laughing matter. N Engl J Med 1992;327:1026–7.

58. Gray RH. Nitrous oxide and fertility. N Engl J Med 1993;328:284.

59. Rowland AS, Baird DD, Weinberg CR. Nitrous oxide and fertility (reply). N Engl J Med 1993;328:284.

60. Brodsky JB. Nitrous oxide and fertility. N Engl J Med 1993;328:284–5.

61. Baird PA. Nitrous oxide and fertility (reply). N Engl J Med 1993;328:285.

62. Ahlborg G Jr, Axelsson G, Bodin L. Shift work, nitrous oxide exposure and subfertility among Swedish midwifes. Int J Epidemiol 1996;25:783–90.

63. Gonen O, Shulman A, Ghetler Y, Shapiro A, Judeiken R, Beyth Y, Ben-Nun I. The impact of different types of anesthesia on in vitro fertilization-embryo transfer treatment outcome. J Assist Reprod Genet 1995;12:678–82.

64. Beilin Y, Bodian CA, Mukherjee T, Andres LA, Vincent RD Jr, Hock DL, Sparks AET, Munson AK, Minnich ME, Steinkampf MP, Christman GM, McKay RSF, Eisenkraft JB. The use of propofol, nitrous oxide, or isoflurane does not affect the reproductive success rate following gamete intrafallopian transfer (GIFT). Anesthesiology 1999;90:36–41.

65. Knill-Jones RP, Newman BJ, Spence AA. Anaesthetic practice and pregnancy. Lancet 1975;2:807–9.

66. Buckley DN, Brodsky JB. Nitrous oxide and male fertility. Reprod Toxicol 1987;1:93–7.

67. Louis-Ferdinand RT. Myelotoxic, neurotoxic and reproductive adverse effects of nitrous

oxide. Adverse Drug React Toxicol Rev 1994;13:193–206.

68. Shnider SM, Webster GM. Maternal and fetal hazards of surgery during pregnancy. Am J Obstet Gynecol 1965;92:891–900.

69. Mellin GW. Comparative teratology. Anesthesiology 1968;29:1–4.

70. Corbett TH, Cornell RG, Endres JL, Lieding K. Birth defects among children of nurse-anesthetists. Anesthesiology 1974;41:341–4.

71. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol 1989;161:1178–85.

72. Kallen B, Mazze RI. Neural tube defects and first trimester operations. Teratology 1990;41:717–20.

73. Sylvester GC, Khoury MJ, Lu X, Erickson JD. First-trimester anesthesia exposure and the risk of central nervous system defects: a population-based case-control study. Am J Public Health 1994;84:1757–60.

74. Heinonen OP, Sloan D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton, MA: Publishing Sciences Group, 1977:358–60.

75. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 1998;4:460–3.

76. Mennerick S, Jevtovic-Todorovic V, Todorovic SM, Shen W, Olney JW, Zorumski CF. Effect of nitrous oxide on excitatory and inhibitory synaptic transmission in hippocampal cultures. J Neurosci 1998;18:9716–26.

77. Jevtovic-Todorovic V, Beals J, Benshoff N, Olney JW. Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain. Neuroscience 2003;122:609–16.

78. Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW. A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. Brain Res 2001;895:264–7.

79. Olney JW, Wozniak DF, Farber NB, Jevtovic-Todorovic V, Bittigau P, Ikonomidou C. The enigma of fetal alcohol neurotoxicity. Ann Med 2002;34:109–19.

80. Jevtovic-Todorovic V, Benshoff N, Olney JW. Ketamine potentiates cerebrocortical damage induced by the common anaesthetic agent nitrous oxide in adult rats. Br J Pharmacol

2000;130:1692–8.

81. Olney JW, Farber NB, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C. Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain. Environ Health Perspect 2000;108(Suppl 3):383–8.

82. Olney JW, Wozniak DF, Jevtovic-Todorovic V, Farber NB, Bittigau P, Ikonomidou C. Drug-induced apoptotic neurodegeneration in the developing brain. Brain Pathol 2002;12:488–98.

83. Ikonomidou C, Bittigau P, Koch C, Genz K, Hoerster F, Felderhoff-Mueser U, Tenkova T, Dikranian K, Olney JW. Neurotransmitters and apoptosis in the developing brain. Biochem Pharmacol 2001;62:401–5.

84. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003;23:876–82.

85. Ratzon NZ, Ornoy A, Pardo A, Rachel M, Hatch M. Development evaluation of children born to mothers occupationally exposed to waste anesthetic gases. Birth Defects Res Part A Clin Mol Teratol 2004;70:476–82.

86. Harrison RF, Shore M, Woods T, Mathews G, Gardiner J, Unwin A. A comparison study of transcutaneous electrical nerve stimulation (TENS), Entonox, pethidine + promazine and lumbar epidural for pain relief in labor. Acta Obstet Gynecol Scand 1987;66:914.

87. Marx GF, Katsnelson T. The introduction of nitrous oxide analgesia into obstetrics. Obstet Gynecol 1992;80:715–8.

88. Irestedt L. Current status of nitrous oxide for obstetric pain relief. Acta Anaesthesiol Scand 1994;38:771–2.

89. Ross JAS, Tunstall ME, Campbell DM, Lemon JS. The use of 0.25% isoflurane premixed in 50% nitrous oxide and oxygen for pain relief in labour. Anaesthesia 1999;54:1166–72.

90. King R, Hepp M. Isoflurane Entonox mixtures for pain relief during labour. Anaesthesia 2000;55:711.

91. Ross JAS. Isoflurane Entonox mixtures for pain relief during labour (reply). Anaesthesia 2000;55:711–2.

92. Stefani SJ, Hughes SC, Shnider SM, Levinson G, Abboud TK, Henriksen EH, Williams V, Johnson J. Neonatal neurobehavioral effects of inhalation analgesia for vaginal delivery.

Anesthesiology 1982;56:351–5.

93. Abboud TK, Swart F, Zhu J, Donovan MM, Peres Da Silva E, Yakal K. Desflurane analgesia for vaginal delivery. Acta Anaesthesiol Scand 1995;39:259–61.

94. Baxi LV, Petrie RH. Pharmacologic effects on labor: effects of drugs on dystocia, labor, and uterine activity. Clin Obstet Gynecol 1987;30:19–32.

95. Datta S, Ostheimer GW, Weiss JB, Brown WU Jr, Alper MH. Neonatal effect of prolonged anesthetic induction for cesarean section. Obstet Gynecol 1981;58:331–5.

96. Jacobson B, Nyberg K, Eklund G, Bygdeman M, Rydberg U. Obstetric pain medication and eventual adult amphetamine addiction in offspring. Acta Obstet Gynecol Scand 1988;67:677–82.

97. Polvi HJ, Pirhonen JP, Erkkola RU. Nitrous oxide inhalation: effects on maternal and fetal circulations at term. Obstet Gynecol 1996;87:1045–8.

98. Bodin L, Axelsson G, Ahlborg G Jr. The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age. Epidemiology 1999;10:429–36.

99. Tomlin PJ. Health problems of anaesthetists and their families. Br Med J 1979;1:1280–1.

100. Zack M, Adam HO, Ericson A. Maternal and perinatal risk factors for childhood leukemia. Cancer Res 1991;51:3696–701.

101. Dale O, Husum B. Nitrous oxide: at threat to personnel and global environment? Acta Anaesthesiol Scand 1994;38:777–9.

102. Jones HE, Balster RL. Inhalant abuse in pregnancy. Obstet Gynecol Clin North Am 1998;25:153–67.

103. Hale TW. Anesthetic medications in breastfeeding mothers. J Hum Lact 1999;15:185–94.